The plasma membrane is
a highly active entity. It exchanges information,
ions, and organic molecules. It may extend, participate in movement and butt off
pieces of itself. In this clip, we're
looking more closely at phagocytosis as a
defense mechanism. Here we see nores rendering of phagocytic cell
capturing some particle, maybe a bacterium. You can see that the
cell has attached to the particle and is
reaching several arms around it that will eventually engulf the particle
in some endosome. Amoeba use this as a
feeding mechanism. When phagocytosis is not
followed by digestion, it may initiate a mutualistic
symbiotic relationship. However, we're interested
in immune function. Many different immune cells take in material
through some form of phagocytosis or endocytosis and metabolize it and
render it harmless. We're going to look at the
three cell types that do most of the phagocytosis
of bacteria. First, we have the neutrophil, our champion first on
the scene protector. We have a macrophage, which is also very
important in this. Finally, we have a
sentinel dendritic cell. Sentinel dendritic cell really isn't there so much
to protect you by phagocytosis as it is
to gather information from the environment and
pass that on to TH cells. When it comes to getting
rid of bacteria, we're really looking at
neutrophils and macrophages. The neutrophils are your
first line of defense, and they can phagocytize and secrete defensive compounds
and even break up to trap the pathogen in a
net like structure. Macrophages also
phagocytize pathogens, as well as debris from
self cell apoptosis, and they also present
antigen to TH cells, so they're helping
out the sentinel dendritic cells there as well. Here's an illustration showing
the sequence of events
of phagocytosis. We're going to take a
closer look at this first one where the
bacterium is captured. Here you can see in
the enlargement, that the phagocyte has
attached to the bacterium, and it's done this using
various receptors. Now, some of those receptors are toll-like receptors
and the phagocytes, both macrophages and
dendritic cells are richly supplied with toll like receptors in their
plasma membranes. In addition, they have Fc receptors so that
they can also recognize and attach to any
antibodies that have been synthesized and can
recognize this bacteria. This attachment activates
actin microfilaments, and the actin
microfilaments will then power those
arms to come around the bacterium and basically
grab it and internalize it. So here we have the
bacterium in an endosome, a phagosome, and we're going
to go and enlarge that one. This way, you can see
those microfilaments are still forming a cage
around the outside of it. Notice the bacterium is now trapped This triggers
a number of events. An important event is the activation of the
membrane of the phagosome. This is going to prompt it
to fuse with a lysosome, and here we're going
to see that in the diagram and enlarge
that one as well. Here's our phagosome. It's actually picked up. We can see one
lysosome. It's about to pick
up another one, and this is going to trigger
hopefully a series of lethal changes in the interior
of this phagolysosome. The membranes begin
to pump hydrogen ions into the interior and that

will acidify the phagosome. They'll pump potassium into the interior and that will
increase its osmotic pressure. As the membranes fuse, they will pick up
toll like receptors, the ones that are part of
the endosomal membrane that help to monitor exactly what pathogen we have captured in this
particular phagolysosome. These toll-like receptors
will then begin to signal the nature
of the threat, and so the cell will begin to activate other inflammatory
responses as well. Also, the increasing
osmotic pressure will cause the
granules to disperse. Now, these are granules with protein in it and
when they disperse, they release active enzymes
and peptide toxins. These changes to
the membrane also trigger an event called
the respiratory burst. You can see here we have
a membrane complex called NADPH oxidase that is embedded in the
phagolysosomal membrane. This is going to take up
oxygen from the outside, and it's going to
release hydrogen ions on the inside as well as we will see other
defensive compounds. When the complex
picks up oxygen, the oxygen picks up an electron, and that turns it into a supercharged highly
reactive superoxide radical. Note that this is released
into the cytoplasm, but this is something
that can diffuse across the membrane very easily
to all parts of the cell. This will react in the
phagolysosome to produce hydrogen peroxide and also
hypochlorous acid or bleach. You have probably used
both of these yourself. You probably used
hydrogen peroxide on a cut to make sure
it doesn't infect, and you've probably
used bleaching your laundry not only
to make it wider, but to make sure you
kill off any bacteria or any other gross things that
might be growing there. In addition to that, a more complex process
requiring synthesis of new enzymes results
in the production of even more toxic
reactive species, the reactive nitrogen species. Here is a table summarizing the most
significant players in this. The reactive nitrogen species
includes nitrous oxide, a variety of sulfur
containing compounds, which are really very deadly
and peroxynitrous acid or its anion. All of these are highly toxic, which explains why
neutrophils in general can only phagocytize about 20 bacteria before they get killed by their very
own defense mechanisms. Meanwhile, back in the
phagolysosome interior, further horrors await the
phagocytose bacterium. Here we're going to
enlarge this again, and you can see that the cell is already beginning
to break up. It's still surrounded by this cage of actin
microfilaments, and the granules have dispersed and are now actively
attacking the cell. If you will recall, when we put potassium into this phagolysosome, it helped to disperse
these granules, and that also increase the osmotic pressure in the phagolysosome which, of course, is why we need all
those microfilaments to keep it from expanding and diluting down the
deadly substances that we're about to
continue to produce. Hydrolytic enzymes will begin
to attack the bacterium. Here we have a list proteases. There's one called
cathepsin, but there are a bunch
of different proteases, varieties with
different specificities that different bacteria

are sensitive to. Lipases, so we can break
up the bacterial membrane. In addition to that,
we have more toxins. Recall, we talked
about lactoferrin before that ties up the iron
that these creatures need. We have defenses. We have a very wide variety of
things that are generally
called defensins. What they do is they
insert themselves into the plasma membranes of the bacteria and
poke holes in it, which helps to kill them. There's also BPI, lipid binding
protein, which binds the lipids and disrupts
the membrane structure. You can see that there is a highly varied attack on
whatever turned up in
this phagolysosome. You might at this point, consider all the ways in which we
kill the microbes we capture. We trap them in a
reinforced phagolysosome at elevated osmotic pressure. We acidify the internal
environment to help pickle them. We flood them with
poisonous reactive oxygen and nitrogen compounds. We add other toxic compounds
and lytic enzymes and
multiple versions of them for pets sake. It sounds like overkill if only. There
is a reason we have so many different versions
of our killing options, and that's because
microbes constantly evolve defenses
against our defenses. They develop
microbial resistance. We wind up playing
microbial whack a mole, and the perfect visual
metaphor for this is John Tenles illustration from Luis Carols through
the looking glass. Alice and the Red Queen
run mad and at the end, wind up in the same place. The Queen informs Alice
that you have to run as hard as you can
just to keep up. Indeed, there are microbes
that can survive all of this. TB bacteria can actually
hitch a ride inside of macrophages and use them for transport to infect far
flung regions of the body. When your body receives
inflammatory signs, your phagocytes up
their toxic production. But like all your other
physiological decisions, they must balance your needs, and this response will be
less effective if you
are malnourished. Deaths in the United States from tuberculosis drop
significantly in the first half of
the 20th century as social programs raise the
overall standard of living. I want to close with a reminder that our shuns from
the first lecture. Nutrition, sanitation,
vaccination, habitation are the
societal measures that support your immune health.